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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/936,985 | 12/19/2001 | Carine Capiau | B45182 | 2966 |

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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

DATE MAILED: 05/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/936,985 | CAPIAU ET AL. | |
| | Examiner | Art Unit | |
| | Vanessa L. Ford | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6-9,11,12,14 and 15* is/are pending in the application.

4a) Of the above claim(s) *12,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 21, 2005 been entered. Applicant's amendment is acknowledged. Claims 1-4, 6, 9 and 11 have been amended.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

### *Rejection Withdrawn*

3. In review of Applicant's remarks the rejection of claims 1-4, 6, 9 and 11 under 35 U.S.C. 112, first paragraph is withdrawn.

***Objection/Rejection Maintained***

4. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-4, 6-9 and 11 for the reasons set forth on pages 2-6, paragraph 3 of the Final Office Action.

The rejection was on the grounds that Kuo et al teach a composition comprising immunogenic polysaccharide-protein conjugates and pneumolysin protein of *Streptococcus pneumoniae* (see the Abstract). Kuo et al teach that capsular polysaccharides of various pneumococcal types (for example, types 6B, 14C, 18C and 20) are used in their inventions (column 5, lines 17-28 and column 6, Example 1). Kuo et al teach that the composition may be added to immunologically acceptable diluents or carriers in the conventional manner to prepare injectable liquid solutions or suspensions (column 5, lines 45-47). Kuo et al teach that the conjugates of the invention may be bound to aluminum hydroxide, aluminum phosphate (alum), QS-21, monophosphoryl lipid A and deacylated monophosphoryl lipid A (which induce strong TH1 responses) (column 5 lines 47-51). It is well known in the art to add protein carriers such as keyhole limpet haemocyanin (KLH), diphtheria toxoid, tetanus toxoid and protein derivative of Tuberculin (PPD) to antigens to enhance the immunogenicity of the antigen this is evidenced by *(U.S. Patent No. 6,419,932, U.S. Patent No. 4, 761, 283, U.S. Patent No. 6,224,880 and U.S. Patent No. 5,360,897).*

Kuo et al do not teach choline binding proteins.

Masure et al teach a vaccine comprising choline binding proteins (CBPs) (column 6, lines 65-67 and column 7, lines 1-8). Masure et al teach vaccines comprising CBP antigen or antigenic derivative or fragment thereof or a CBP nucleic acid vaccine that can be administered via any parenteral route including but not limited to intramuscular, intraperitoneal, intravenous and the like (column 24, lines 57-61). Masure et al suggest that criteria to consider in selecting a preferred CBP as a vaccine candidate includes testing CBP defective mutants for attenuation of virulence in animal models for bacteremia or colonization efficacy alone or in combination or coupled to a capsular polysaccharide (column 14, lines 41-46). Masure et al teach that the vaccines of the invention can be comprises an active material such as a diluent (i.e. carrier or vehicle) (column 29, lines 14-20). Masure et al teach that CBP or fragment thereof can be conjugated to an immunogenic carrier, e.g. bovine serum albumin (BSA) or keyhole limpet hemocyanin (KLH) (column 22, lines 5-8).

It would be *prima facie* obvious at the time the invention was made to add the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection, including but no limited to antibiotics, soluble carbohydrate inhibitors of bacterial adhesion, other small molecule inhibitors of bacterial adhesion, inhibitors of bacterial metabolism, transport or transformation,

stimulators of bacterial lysis or antibacterial antibodies or vaccines directed at other bacterial antigens (column 30, lines 34-42). It would be expected barring evidence to the contrary, that the addition of the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al would be effective in treating *Streptococcus pneumoniae* infections.

Applicant urges that it is known in the art that the more complex a vaccine is the more immune interference can be an issue between components resulting a bad product. Applicant urges is no motivation to combine teachings of Kuo et al with Masure et al with a reasonable expectation of success. Applicant urges that a skilled person in the art would not have selected a Th1 adjuvant from all the different types of adjuvants used in Kuo et al. Applicant urges that there is no motivation to connect all of the elements. Applicant urges that to establish a *prima facie* case of obviousness there must a suggestion or incentive that would motivate one skilled in the art to modify a reference or combination of references. Applicant urges that Kuo et al teach that Th1 adjuvants as well as Th2 adjuvants can be used in the vaccine compositions and only aluminum phosphate is used in the examples. Applicant urges that the Examiner is using hindsight reconstruction because absent the teachings of the instant specification, a skilled person would never had combined the teachings of Kuo et al and Masure et al to confer a value added benefit that would overcome the feeling of potential risk of product complexity that the skilled person would have had.

Applicant's arguments filed March 21, 2005 have been fully considered but they are not persuasive. It is the position of the Examiner that the claims recite "comprising" which is open claim language. Therefore, the claimed elements may be comprised in

the claimed composition along with any other elements. In other words, the claims are no so limited to the *Streptococcus pneumoniae*-protein conjugates, unconjugated *Streptococcus pneumoniae* antigen and an adjuvant which is a preferential inducer of a TH1 response. Thus, the combination of prior art references teach that Th1 adjuvants and/or Th2 adjuvants may be included in the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would be motivated to use the *Streptococcus pneumoniae* polysaccharide-protein conjugate and an adjuvant, for example, a preferential inducer of a TH1 response as taught by Kuo et al in combination with the *Streptococcus pneumoniae* protein antigen (choline binding proteins) of Masure et al because both have been shown to be protective against *Streptococcus pneumoniae* infections. It should be noted that Masure et al teach that the choline binding proteins mediated adhesion. One of ordinary skill in the art would be motivated to add choline binding proteins to other vaccine components to prevent bacteria from adhering to the cell surface, thereby preventing infection. If a bacterium cannot adhere to the cell surface then infection is minimized. One of ordinary skill in the art would have been motivated to

use a TH1 adjuvant because these adjuvants have been shown to be effective as adjuvants in *Streptococcus* vaccine compositions. The vaccine composition as taught by Kuo et al are used to target infections caused by *Streptococcus pneumoniae*. Therefore, a vaccine composition comprising the choline binding proteins as taught by Masure et al and the polysaccharide-protein conjugates and adjuvants as taught by Kuo et al can be use as multi-component, multi-purpose vaccines for protection against pneumococcal infections. One skill in the art would reasonably be motivated to combine multiple pneumococcal antigens in a vaccine against *Streptococcus pneumoniae* infection because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection, including but no limited to antibiotics, soluble carbohydrate inhibitors of bacterial adhesion, other small molecule inhibitors of bacterial adhesion, inhibitors of bacterial metabolism, transport or transformation, stimulators of bacterial lysis or antibacterial antibodies or vaccines directed at other bacterial antigens. Therefore, there is no reason to believe that a vaccine comprising multiple components will result "immune interference" or result in a "bad product" as asserted by Applicant.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

5. The objection to claim 11 is maintained for the reasons set forth on page 6, paragraph 4 of the Final Office Action.

The rejection was on the grounds that claims 11 is objected to because it depends from"... any one of claims1-9". It should be noted that claim 5 has been cancelled. Therefore, the claim depends from a cancelled claim because claim 5 is included in the phrase "any one of 1-9". Correct is required.

Applicant did not respond to this objection and therefore, the objection is maintained.

***New Ground of Rejection***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 6-9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for at least one *Streptococcus pneumoniae* polysaccharide-protein antigen and at least one unconjugated

*Streptococcus pneumoniae* protein antigen, does not reasonably provide enablement for transmembrane deletion variants of PspA, PsaA or CbpA.

Claims 1-4, 6-9 and 11 are drawn to an immunogenic composition comprising at least one *Streptococcus pneumoniae* polysaccharide-protein conjugate, at least one unconjugated *Streptococcus pneumoniae* protein antigen and an adjuvant which is a preferential inducer of a TH1 response.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification recites *Streptococcus pneumoniae* polysaccharide antigens 1-5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 20 22F, 23F and 33F are contemplated by the claimed invention (page 12). The specification recites *Streptococcus pneumoniae* protein antigens pneumolysin, PsaA, PspA, PspC, CbpA or a combination of two or more of such proteins which are used in the claimed invention (page 13).

The specification is not enabling for transmembrane deletion variants of pneumolysin, PsaA, PspA, PspC, CbpA . The specification only incorporates by reference the teachings of how to make and use the *Streptococcus pneumoniae* polysaccharide antigens and *Streptococcus pneumoniae* protein antigens of the claimed invention. The specification does not disclose, What amino acids are involved in the transmembrane deletion variants of pneumolysin, PspA, PspC, PsaA, glyceraldehyde-3-phosphate dehydrogenase or CbpA?

There is no guidance provided as to which amino acids can be deleted and still have the protein retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple deletions. The sequence of

some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such proteins.

Prior art regarding amino acid modifications is cited below:

Thomas E. Creighton, in his book, *"Proteins: Structures and Molecular Properties, 1984", (pages 314-315)* teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Praline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins

appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to transmembrane deletion variants having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make transmembrane deletion variants of the claimed *Streptococcus pneumoniae* polysaccharide antigens and *Streptococcus pneumoniae* protein antigens in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation to is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation

with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

***Status of Claims***

7. No claims allowed.

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272–0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 24, 2005

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